PATENT APPLICATION
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IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

In re Application of: Boris Masinovsky et al. Serial No: 08/448,649 Filed: May 24, 1995 For: Methods for Using Agents that Bind to VCAM-1 (Amended Title) Group Art Unit: 1815 Examiner: P. Gambel, Ph.D.	I hereby certify that this paper is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on DATE:_____ _____ Li-Hsien Rin-Laures, M.D. Registration No. 33,547 Attorney for Applicants

DECLARATION OF BEVERLY J. TOROK-STORB, Ph.D., UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Beverly J. Torok-Storb, Ph.D., hereby declare as follows that:

1. I received a B.S. in biology and secondary education in 1970 and a master's degree in aquatic biology in 1971 from Edinboro State College, Edinboro, Pennsylvania. I received a Ph.D. in radiation biology and human genetics in 1975 from the University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania. From 1975 to 1976 I was a Senior Fellow at the University of Washington Department of Pathology, Seattle, Washington. At the University of Washington School of Medicine, I was a Senior Fellow at the Department of Hematology from 1976 to 1979, a Research Assistant Professor of Medicine from 1979 to 1985, a Research Associate Professor of Medicine from 1985 to 1991, and a Research Professor since 1991. At the Fred Hutchinson Cancer Research Center, Seattle, Washington, I was an Associate in Medical Oncology from 1978 to 1980, an Assistant Member from 1980 to 1984, an Associate Member from 1984 to 1991, and a Member since 1991.

I am an author or co-author of over 85 scientific publications. My honors and activities include: a National Research Service Fellowship Award from NIAMDD in 1977; a Special Fellowship from the Leukemia Society of America in 1979; a Young Investigator Award from NHLBI in 1979; Chairman of Clinical Sciences Study Section 4 (CLN4), National Institutes of Health (NIH), from 1985 to 1988; Member of the NIH Reviewer's Reserve from 1988 to 1992; Visiting Professor at the Canadian Royal Academy of Physicians and Surgeons in 1989; Visiting Professor at the University of Ulm, Ulm, Germany in 1990; Chairman of the Scientific Committee ISEH meeting in Seattle in 1990; Member of the Science Advisory Council, Pacific Science Center in 1990.

2. I have reviewed the above-identified patent application U.S. Serial No. 08/448,649, including the currently pending claims, and the Office Action issued March 21, 1995 in the prior application U.S. Serial No. 08/051,455. As a result of my scientific training and experience, I am knowledgeable about bone marrow transplantation and about the interactions between bone marrow cells and bone marrow stromal cells. I am therefore qualified to discuss what one of ordinary skill in the art of bone marrow transplantation would understand from the statements made in the application.

3. I make the following statements to respond to the Examiner's concerns regarding how the claimed methods promote bone marrow transplantation, and what therapeutic benefit would be provided by inhibiting the interaction between bone marrow cells and bone marrow stromal cells. Specifically, I respond to the statements at page 4 of the Office Action to the effect that:

> In addition, it is not clear what is the therapeutic benefit of decreasing adhesion of bone marrow cells to bone marrow stromal cells. The disclosure appears to indicate the use of the instant 6G10 antibody either to ameliorate inflammatory conditions (Summary of the Invention), the claims of which have been canceled; or to promote bone marrow transplantation (Example 5). How do the claimed methods promote bone marrow transplantation or hemopoiesis?

4. Briefly, bone marrow transplantation involves the following steps. Bone marrow is harvested from the donor by direct aspiration from the bone. This bone marrow may be subjected to various procedures to render it enriched in primitive stem cells and hematopoietic progenitor cells. The recipient's immune system is destroyed to prepare the recipient for transplantation. This destruction is accomplished either through total body irradiation, chemotherapy (*e.g.*, cyclophosphamide treatment), or administration of anti-thymocyte globulin (which binds to and facilitates the destruction of the recipient's lymphocytes via the recipient's own complement system). The donor's bone marrow cells are then infused intravenously into the recipient's bloodstream.

5. One of ordinary skill in the art of bone marrow transplantation as of August 2, 1990 (which I have been advised is the effective filing date of this application) would understand from reading the application, particularly at pages 4 and 17, that the Applicants had made a novel finding that VCAM-1 is expressed on human bone marrow stromal cells. Further, the ordinarily skilled person would understand from the application that VLA-4 (a major receptor for VCAM-1) is expressed at high levels on bone marrow cells, particularly on a subset enriched in primitive stem cells and progenitor cells, and that adhesive interactions between this subset of bone marrow cells and bone marrow stromal cells may be mediated by VCAM-1. For example, at page 17, lines 11-14 and 24-33, the application states:

> The IL4/TNFα-enhancement of 6G10-recognized antigen expression on the stromal cells is evident in panel A. This novel finding would not have been predicted a priori from available information about the tissue distribution of VCAM-1.
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> . . . .
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> Further, we have discovered that a major receptor for VCAM-1, VLA-4 (also known as integrin alpha4/beta1 (69)), is expressed at high levels on bone marrow cells bearing the CD34 antigen. . . . This finding of coexpression is significant because CD34 expression distinguishes a subset of bone marrow cells (1-4%) which are enriched in primitive stem cells and progenitors (70). Therefore, we infer that adhesive interactions within the bone marrow between hemopoietic stem cells and/or progenitor cells and stromal elements may be mediated by the binding of VLA-4 and the antigen recognized by 6G10.

With this knowledge and the further information reported in the application (*e.g.*, at pages 4 and 15) that anti-VCAM-1 antibodies such as 6G10 would block VCAM-1-mediated adhesive interactions, one of ordinary skill in the art would understand that anti-VCAM-1 antibody would be useful for blocking VCAM-1-mediated binding of bone marrow stromal cells and bone marrow cells.

6. One of ordinary skill in the art, after being informed of the discovery of VCAM-1 expression on bone marrow stromal cells, would have understood from the disclosure in the application that a clear therapeutic benefit of administering anti-VCAM-1 antibody to decrease adhesion of bone marrow cells to bone marrow stromal cells would be the interruption of progenitor/stroma binding and consequential release of bone marrow cells into the bloodstream. This antibody-mediated release of bone marrow cells would allow those cells to be harvested directly from the blood of a donor. The advantages attendant upon this harvesting method are numerous: it is easier to harvest cells from blood than from bone marrow, the cells harvested are already conditioned to be in the blood (a desirable attribute because donor bone marrow is infused into the recipient's bloodstream), and the cells released are already enriched in primitive stem cells and progenitor cells. One of ordinary skill in the art would likely view an antibody-mediated decrease in bone marrow cell adhesion to be a therapeutic method more easily employed in donors than in recipients, because the mere release of bone marrow cells is an adequate therapeutic endpoint with regard to harvest from the donor. In contrast, an additional destructive step (destroying the immune-related bone marrow cells and other cells of the immune system using means known in the art) would need to accompany treatment of the recipient. In combination with such destructive means, the antibody-mediated release of bone marrow cells would also have been understood to have therapeutic benefit in recipients.

7. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Date: 12/7/95

Beverly J. Torok-Storb, Ph.D.